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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/523,809	03/13/00	MURPHY M	686.03.498C0

EXAMINER	
KAUSHAL,S	
ART UNIT	PAPER NUMBER
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DATE MAILED: 07/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/523,809	MURPHY ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 04/16/01 and Dr. Parenteau declaration under 37 CFR 1.132 have been fully considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC ' 112

In response to applicant' s remarks and Dr. Parenteau declaration, the rejection of claims 1-30 under 35 USC 112 (1) is withdrawn.

The declaration of Dr. Parenteau under 36 CFR 1.132 is fully considered and is found persuasive. The declaration clearly teaches that the morphology of tissue construct grown with or without supplementation is identical (see exhibit B). Furthermore, making of culture tissue constructs comprising dermal papilla of hair follicle and three layer tissue construct is found enable in view of applicants remarks file on page 14 of the response. In addition, applicant remarks that genetically engineered cells which produce extracellular matrix components is within the skill in the art is found persuasive.

Claims 1-30 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons of record as set forth in the official action mailed on 10/12/00.

The applicant argues that exogenous matrix components are matrix components not produced by the cultured cell but are introduced by other means. However, this is not found persuasive because it is unclear what is the nature (chemical or biological structure) of

"exogenous matrix components". Similarly, it is unclear what is encompassed by "synthetic members". The broadest reasonable interpretation of a synthetic member encompass any non-naturally occurring polymer and any and all types of tissue supports.

Claims 7 and 21 are unclear as to the metes and bounds of a culture medium containing "no non-human components". The applicant argues that "no non-human component" are component without the use of undefined or non-human-derived biological components such as bovine serum or organ extract. However, this is not found persuasive because it is still unclear does this include any chemical or protein, to include essential and non-essential amino acids, which are not produced in the human body or required for its proper functioning?

Claims 19-23 and 24-26 are unclear as to the steps involved in "stimulating the fibroblast cells to synthesize, secrete, and organize extracellular matrix components". The applicant argues that step as claimed are well known to those skill in the art and the specification also teaches that culture is supplemented with components that assist matrix synthesis (response, page 16, sec. D). However, this is not found persuasive because the invention as claimed fail to recite the required step.

Claims 1-18, 28 and 30 are unclear as to the metes and bounds of cultured "under conditions to produce a layer of extracellular matrix". The applicant argues that one skill in the art would under stand the scope of this claim language in the light of specification (response, page 16, sec. D). However, this is not found persuasive because it is unclear what are the conditions in this context.

Claim Rejections - 35 USC ' 103

Claims 1-3, 6-12, and 19-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bell, E. (US Patent 4,485,096), Parenteau et al (US Patent 5,712,163), Sand, BJ (US Patent

5,618,284) and Holbrook et al (1993) and Biegel et al (1994) for the same reasons of record as set forth in the official action mailed on 10/12/00.

The applicant argues that the patentable distinction between Bell and instant invention is that Bell requires the use of hydrated lattice or an exogenous matrix component. Applicant argues that Parenteau does teach a chemically defined cell culture medium but does not teach or suggest instantly claimed invention. The applicant further argues that Parenteau does not teaches the absent of exogenous matrix components and synthetic components. The applicant further argues that Sand and Holbrook states what is know in the art regarding human type-I collagen and dermal matrix of connective tissue respectively. The applicant further argues that Biegel does not describe coating transwell filters with hydrated collagen gels then culturing endothelial cells. The applicant further argues that instant invention as claimed is not rendered obvious by the cited references (response, page 17, sec. III).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Bell, E teaches the use *in vitro* of human foreskin and dermal fibroblasts cultured in Falcon bacteriological dishes comprising McCoy's 5a medium, Fetal Calf Serum, NaOH, and a collagen solution to form a contractable, transplant tissue and wherein a layer of keratinocytes may be added *in vitro* (claims 15 & 16; and Example 1, col 8, lines 39-55, col 3, lines 28-30). Bell also teaches the method of tissue transplantation in guinea pigs and rats (e.g. Examples 10 and 11). Bell et al does not teach the use of chemically defined media, the molecular composition of the differentiated tissue, e.g. collagen, decorin, and GAG, or the use of said procedure in the absense of exogenous matrix components (e.g. collagen).

Parenteau et al teach the use of a chemically defined cell culture medium, which by definition are absent of undefined proteins from protein supplements such as serum, and wherein the cell culture systems comprise said cell culture medium and a substrate for the cells, **such as glass or plastic**, and in the absence of exogenous matrix components or synthetic membranes which resulted in the prolonged growth and differentiation of cells, such as keratinocytes,(e.g. col 1, lines 35-55, claims 20 and 24). Parenteau et al also teach the culturing of human karatinocytes on plates NOT coated with collagen (col.24, example-5). Parenteau et al also teach the method of producing skin equivalents grafts in vitro utilizing keratinocytes and dermal (fibroblast) equivalents (example 6, col 25, line 61-col 26, line 14), and the use of a sequential two culture medium process in the absence of a substrate which showed only a slight decrease in plating efficiency in comparison to those that were grown on a collagen substrate (e.g. Table 5, col 5).

In addition, Sand, BJ teaches that human type-1 collagen molecule consists of chains of 300 nm triple helixes joined by 67 nm uncoiled bonds (col 10, lines 32-33). Holbrook et al teach that the dermal matrix of connective tissue is comprised of collagen, of which 80-90% is type I and 8-12% is type III, glycosaminoglycan, fibronectin, and tenascin (pg 117, col 1, para 3 & pg 119, col 1, para 1 and 3). Biegel et al teach the use of the Transwell filters coated with hydrated collagen gels for the use in growing endothelial cells in vitro which resulted in monolayers growing until confluency and exhibiting biochemical, morphological, and electrophysiological properties reflective of cells in vivo (abstract).

In light of Bell, Parenteau, Sand, Holbrook and Biegel et al it would have been obvious to one of ordinary skill in the art to make a cultured tissue construct comprising fibroblast cells, such as neonate male foreskin or dermal, grown under a sequential cell culture conditions on a Transwell plate coated with collagen to produce a layer of extracellular matrix comprising type I and III fibrillar collagen, glycosaminoglycan, decorin, fibronectin, and tenascin and wherein said cells are cultured in the absence of exogenous matrix components in a chemically defined media containing no non-human components and comprising a second layer of epithelial cells, such as keratinocytes; and utilizing said construct for transplanting in an animal model.

Furthermore, Parenteau teaches that cells can be cultured on **glass or plastic**, and in the absence of exogenous matrix components like collagen. Parenteau et al also teach the culturing of human karatinocytes on plates NOT coated with collagen (col.24, example-5). Furthermore the percentage of cell confluence, the thickness of the resulting matrix, and the density of the seeded cells are rate effective variables which one of ordinary skill in the art could readily ascertain through routine experimentation.

One would have been motivated to utilize a tissue construct in the absence of exogenous matrix components to provide an efficacious method of dermal regeneration which did not require the construction of a biodegradable matrix, and to utilize a chemical defined medium to optimize tissue differentiation and growth (Parenteau et al, col 1, lines 35-55). One would also have been motivated to use a porous membrane, such as Transwell plates, because the layer of collagen (or polycarbonate membrane) on the plates would allow for the efficacious adhesion and differentiation of fibroblast cells, especially in light of the absence of an exogenous extracellular matrix scaffold. There would be a reasonable expectation of success because Bell demonstrated that tissue constructs could be generated utilizing a base layer of fibroblasts with a top layer of keratinocytes to generate full thickness skin grafts and done in the absence of three dimensional matrices (e.g. Bell, claim 16) and because Parenteau et al had demonstrated the successful use of tissue constructs comprising keratinocytes using said defined culture medium and in a sequential two step culture system and without any collagen coating and because Biegel et al had demonstrated the sucessful use of the Transwell system for in vitro growth and differentiation of endothelial cells into tissue (e.g. Parenteau et al, Example 5, col 24, lines 35-40, & Biegel et al, abstract).

Claims 1, 4, 5, 9, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jahoda et al (1993) in view of Parenteau et al (US Patent 5,712,163) for the same reasons of record as set forth in the official action mailed on 10/12/00.

The applicant argues that Jahoda does not teach the creation of a cultured tissue construct comprising cells grown under conditions to produce a layer of extracellular matrix, which is synthesized and assembled by the cultured cells. The applicant further argues that Parenteau do not show the presence in the extracellular matrix of fibrillar colagen showing a packaging organization. The applicant further argues that Parenteau do not show tissue construct comprising fibroblast grown on extracellular matrix produced by the cultured fibroblasts. The applicant further argues that Parenteau does not teach absence of exogenous matrix components and synthetic components. The applicant concluded that it would not have been obvious to one ordinary skill in the art a the time of invention to a tissue culture construct as claimed wherein the extracellular matrix is produced in the absence of exogenous matrix component or such a construct wherein the cultured cells are dermal papilla cells.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Jahoda et al teach that the transplantation of dermal papilla cells in rat ear wounds resulted in the production of hair growth in comparison to a control of transplanted skin fibroblasts, which resulted in no new hair growth (abstract and pg 585, col 1, para 1-3 and Table 1). Although, Jahoda et al does not teach the use of a cultured tissue construct system grown in vitro to produce extracellular matrix components, this deficiency is cured by Parenteau.

Parenteau et al teach the use of a chemically defined cell culture medium, which by definition are absent of undefined proteins from protein supplements such as serum, and wherein the cell culture systems comprise said cell culture medium and a substrate for the cells, such as glass or plastic, and in the absence of exogenous matrix components or synthetic membranes which resulted in the prolonged growth and differentiation of cells, such as keratinocytes,(e.g.

col 1, lines 35-55, claims 20 and 24). Parenteau et al also teach the method of producing skin equivalent grafts in vitro utilizing keratinocytes and dermal (fibroblast) equivalents (example 6, col 25, line 61-col 26, line 14), and the use of a sequential two culture medium process in the absence of a substrate which showed only a slight decrease in plating efficiency in comparison to those that were grown on a with or without collagen substrate (e.g. Table 5, col 5).

Thus in light of Jahoda and Parenteau et al, it would have been obvious to one of ordinary skill in the art at the time of the invention to create a cultured tissue construct comprising dermal papilla cells with fibroblast cells and with or without a top layer of epithelial cells, such as keratinocytes. One would have been motivated to do this to provide a method of producing a tissue construct that could be used to generate new hair growth (Jahoda et al, Table 1). There would be a reasonable expectation of success because Jahoda et al demonstrated the ability to culture dermal papilla cells in MEM containing fetal bovine serum and L-glutamine and then transplant them into rats for successful production of hair and the culturing and implantation of fibroblasts for successful production of dermal skin, while Parenteau et al had demonstrated the ability to culture keratinocytes in the absence of exogenous matrix components and synthetic membranes to produce differentiated, stratified tissue (Parenteau et al, abstract).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are required to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED to facilitate further examination.

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